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The Safety of Low-Dose *Larrea tridentata* (DC) Coville (Creosote Bush or Chaparral): A Retrospective Clinical Study

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ABSTRACT

Objective: To determine whether internal use of low doses of *Larrea tridentata* tincture or topical applications of this traditional herbal medicine are safe.

Design: Retrospective review of all people prescribed *Larrea* for internal or for topical use over a 22-month period.

Setting/Location: A general naturopathic practice in Sedona, Arizona.

Subjects: Thirteen patients were identified for whom *Larrea* tincture for internal use was prescribed. An additional 20 female and 3 male patients were identified for whom an extract of *Larrea* in *Ricinus communis* (castor) oil for topical use was prescribed. No patient had any history of liver disease.

Interventions: *Larrea* was prescribed as part of the usual care of each patient. In all cases it was given as either part of a complex herbal formula individualized for each patient containing less than 10% *Larrea* tincture or as an extract in *Ricinus* oil for topical use.

Outcome Measures: Serum liver enzyme levels as well as blood urea nitrogen and creatinine levels, glucose levels, electrolytes, bilirubin levels, iron levels, ferritin levels, lipid levels, and complete blood count (CBC) were available for analysis in four patients; general clinical history and physical examination findings were relied on in all other cases.

Results: The four patients with complete before and after blood chemistry panels and CBC had no indication of liver damage from use of *Larrea*. This included one patient who was taking medications with significant potential for hepatotoxicity. No patient in the study, whether using *Larrea* for short term or long, internally or externally, showed any sign of organ damage during the period of follow-up.

Conclusions: Relatively small intakes of *Larrea* tincture, or topical application of extracts in *Ricinus* oil, are safe when prescribed by a clinically trained botanical prescriber. *Larrea* should be used with caution in persons with a history of previous, or current, liver disease. It may be preferable to avoid the use of *Larrea* capsules because they have been associated with potentially dangerous overdosing.

INTRODUCTION

A series of case reports in the mid-1990s appeared in the literature implicating the leaves, flowers, and twigs of *Larrea tridentata* (DC) Coville (creosote bush or chaparral) as a possible cause of liver damage (Sheikh et al., 1997). *Larrea* has no previously recorded history of causing hepatotoxicity despite wide use as a medicinal plant throughout the south-

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western United States and northern Mexico (Moore, 1989; Brinker 1993/4; Kay, 1996). In fact, it has been described as having a beneficial impact on liver metabolic functions according to empirical use (Moore, 1989). A French patent has been issued on a key ingredient in *Larrea* known as nordihydroguaiaretic acid (NDGA) describing its use for persons with alcoholic liver disease (Oliveto, 1972).

Larrea is an ancient plant, with individual specimens having been carbon dated to an age of approximately 9,000 years (Nabhan, 1985). Others have claimed *Larrea* stands may be as old as 13,000 years (Moore, 1989). These bushes grow to be 6 to 18 feet tall with small, dark green, greasy, leathery leaves that turn bright green after a rain. The small yellow flowers mature into white, fuzzy seed capsules containing five seeds. Creosote is a poisonous, oily liquid obtained by distillation of coal tar that has a scent similar to that of *Larrea*, hence the common name creosote bush. Creosote is otherwise unrelated to *Larrea*. Table 1 shows the constituents found in *Larrea* and their actions where known.

Larrea has been known by several common names besides creosote bush. The name chaparral is perhaps the most common, although this is misleading. Chaparral is an ecological zone where plants are drought-, sun-, and fire-adapted. *Larrea* is an xerophyte (dry land plant) and rarely grows in the chaparral (Nabhan, 1985). Common Spanish names include *hediondilla* ("little smelly one") and *gobernadora* ("governess"). It is called *gobernadora* in part because *Larrea* stands can dominate large regions in the desert at elevations below 4,000 feet.

Larrea has been used as medicine for many centuries. *Larrea* pollen has been identified in coprolites from ancient sites in the southwestern United States (Kay, 1996). Numerous uses have been mentioned for *Larrea* in the ethnobotanical literature (Moore, 1989; Brinker, 1993/4; Kay, 1996; Curtin and Moore, 1997). Only the most common uses and those that appear in multiple sources will be reported here. These uses generally conform to modern clinical experiences with use of *Larrea*. Internally and topically it has been used to treat abdominal complaints with problems in gastrointestinal and pelvic organs including dyspepsia, dysmenorrhea, and premenstrual syndrome. Rheumatic and autoimmune conditions, arthritis, and back pain stand out as common uses of topical *Larrea*. Additional topical uses, particularly of fomentations or powders, are to treat minor wounds, skin infections such as impetigo and chicken pox, and gingivitis. Several

Table 1. *Larrea tridentata* Constituents and Their Actions

Class of constituents	*Specific constituents*	*Reported actions in* Larrea
Lignans	Nordihydroguaiaretic acid (NDGA), norisoguaiacin, dihydroguaiaretic acid, etc.	Antioxidant. Antimicrobial, antifungal, and antiviral. Inhibit electron transport chain in mitochondria. Inhibits phospholipase A_2, cyclooxygenase, and lipoxygenase. Cytotoxic and anticarcinogenic. Hypoglycemic (Luo et al., 1998). Analgesic (Bergel, 1955).
Flavonoid glycosides	Apigenin methyl ester quercetin, dimethoxyl morin (DMM), kaempferol, etc.	Inhibit NADH oxidase, phospholipase A_2, and lipoxygenase. Cytotoxic (DMM). Inhibit replication of RNA viruses.
Triterpene saponins	Larreagenin A, larreic acid, etc.	Unknown
Volatile terpenoids	α-Pinene, limonene, linalol, camphor, benzaldehyde, farnseol, etc.	Unknown
Sterols	β-Sitosterol, campesterol, etc.	Unknown
Protein	Amino acids	Nearly as high quality as alfalfa once resin is removed.
Carbohydrates	Dextrin, glucose, sucrose	Nutritive
Lipids	Wax esters	Unknown
Vitamins	Vitamin C, carotenoids	Nutritive
Minerals	Minerals	Nutritive

Source: Brinker 1993/4, unless otherwise noted. Used with permission of the author.

native peoples used it as deodorizer on the feet and in the armpits. Its internal use is frequently mentioned as a treatment for those with upper respiratory tract viral infections, bronchitis, coughs, urinary tract infections, dyspepsia, abdominal cramps, enteritis, dysentery, and cancer. Finally, it has been reported to improve the quality of blood lipids, apparently supported by clinical trials conducted in Latin America (Moore, 1989). There are historical mentions of use of *Larrea* as an abortifacient, although it was also used as a means to increase fertility (Kay, 1996). Until more information is available, internal use of *Larrea* should be avoided in pregnancy.

Toxicity caused by *Larrea* ingestion is multifactorial in nature. Contributing factors are consumption of excessively large amounts related to the use of encapsulated products, idiosyncratic reactions, and possibly adulteration. The traditional way to take creosote bush is as a tea. The flavor is strong and often considered disagreeable, greatly limiting the amount that can be ingested. Capsules allow people to take much greater amounts easily, and taste is not a limiting factor. Powdered herbs were not traditionally used as medicines for the most part, although it is unclear if *Larrea* in this form is particularly more of a problem than tea or tincture.

An idiosyncratic effect of *Larrea* on the livers of uniquely susceptible individuals also cannot be ruled out. This would, however, suggest the problem was mostly with the patient and not the medicine—idiosyncratic reactions can happen in response to any substance. Supporting this contention is the lack of any study to date that has identified any constituent of *Larrea* that causes the adverse effects seen in reported cases of poisoning *in vitro*, in laboratory animals, or in humans.

Finally, adulteration or contamination of the *Larrea* products reported in other case series cannot be ruled out based on the evidence provided (Sheikh et al., 1997). It is possible that some of the instances of reported *Larrea*-related liver damage were actually caused by microbial contamination (such as aflatoxins) or the presence of some other botanical that actually caused liver damage. In other instances, this has been documented to occur. For example, one report that originally blamed *Scutellaria lateriflora* (American skullcap) for causing liver damage in humans actually turned out to be adulterated with *Teucrium chamaedrys* (germander) or a similar species (MacGregor et al., 1989). Germander contains known hepatotoxic pyrrolizidine alkaloids.

Presented here is a retrospective review of patients seen at our clinic in the past 2 years who were treated with lower doses of *Larrea*. The duration of treatment was variable. In these cases, the leaves and flower were delivered as a tincture (hydroethanolic extract) as 7%–18% of complex formulae including 8–10 other botanical extracts. It is the authors' hypothesis that a tincture more closely approximates the traditional use of *Larrea* as a tea compared to powdered leaves delivered in capsules, and that low doses (less than 1 mL daily) of tincture taken for as long as 5 months are without discernable toxicity. The use of combinations of herbs was also practiced in traditional herbalism, as reflected by this tendency among Hispanics who almost certainly learned the use of local plants from native peoples (Curtin and Moore, 1997). This is true even in persons at substantial risk of developing liver injury, such as one patient who was taking potentially hepatotoxic drugs concomitantly. Data will also be presented to show that topical use of *Larrea* is safe.

A small body of evidence contradicts our theory that aqueous extracts of *Larrea* are nontoxic. One case report involved a woman who drank 3 to 4 cups of *Larrea* tea over a 3-month period along with 5 to 6 cups of *Tabebuia spp.* (taheebo or pau d'arco) bark tea over a 6-month period and developed renal cell carcinoma (Smith et al., 1994). Causation was not proven and it seems unlikely the tumor could have developed over such a short period of time. A worsening or improvement of the cancer cannot be ruled out based on the data in this case report. Three patients of 18 in the *Archives of Internal Medicine* case series who developed adverse effects related to *Larrea* consumed this herb primarily as a tea (Sheikh et al., 1997), however, only 1 of 13 cases with liver toxicity used it in the form of a tea. Precise dose information on the 3 patients with adverse effects who drank *Larrea* tea was not provided. Thus, there is a re-

mote possibility that *Larrea* may entail some risk even when taken as an aqueous extract.

Supporting our hypothesis is a trial in which 59 patients with terminal cancer were given either 16 to 24 ounces of *Larrea* tea or 250 to 3,000 mg NDGA daily (Smart et al., 1970). None of these patients developed jaundice or other signs of liver damage, although some participants reported nausea and vomiting, diarrhea, abdominal cramps, rash, stomatitis, and fever (in order of decreasing frequency). Intramuscular injection of NDGA at a dose of 400 mg/kg daily for as long as 6 months has not been reported to cause liver damage or other toxic effects (Bergel, 1955). This dose, assuming a 10% NDGA content of *Larrea*, would be equivalent to 280 g of leaf daily (approximately 9 ounces of tincture) for a person weighing 70 kg (Brinker, 1993/4). There is evidence that *Larrea* resin (containing NDGA among other phenolic compounds) has antifeedant activity in insects; the application of this information to humans is of unknown importance (Rhoades, 1977). NDGA is therefore an unlikely candidate as a toxic constituent in *Larrea*. Other possible toxic constituents have not been evaluated.

MATERIALS AND METHODS

A computer-generated list of all sales of *Larrea tridentata* in any form from the clinic's dispensary was utilized to identify patients to whom this herb was sold between January 1, 1997 and October 15, 1998. Records on each patient were then cross checked to confirm the prescription and to determine the details of the patient's case. All persons identified were included in the analysis. The maximum possible dose taken was determined based on the amount of product sold; in some cases the patient may not have taken all of the *Larrea* sold to them.

Raw material for *Larrea* tincture was picked from the wild locally and confirmed by organoleptic assay (use of sight, smell, and taste to identify and evaluate the quality of the herb) to be quality specimens for medicinal preparation by one of us (S.H., who has 25 years experience in the field of botanical medicine), on the basis of the presence of resinous coating, morphology, odor, and taste. Only green new growth with flowers present and prior to seed production was selected from healthy looking plants. A voucher specimen was retained on site. The undried leaves and flowers were lightly ground in 90% ethanol and 10% distilled water at a weight-to-volume ratio of 1:2.5. A high ethanol content is used because this most efficiently extracts resinous compounds, particularly NDGA (Duisberg et al., 1949). NDGA extraction in water is low by comparison (Obermeyer et al., 1995). The resultant product was allowed to macerate (soak) for at least 14 days out of direct sunlight. The material was then pressed and filtered to remove any solid sediment and the final tincture packaged in amber glass bottles.

A portion of some raw *Larrea* material was air-dried in a paper bag at room temperature. This technique works only in arid climates such as Arizona. It was mixed with oil from *Ricinus communis* (castor) seed in a weight-to-volume ratio of approximately 1:3. This mix was left to digest at 100° to 115°F for 48 hours. The material was then cooled and pressed to remove solid matter; it was not filtered. The final oil was stored in amber glass bottles.

Twelve patients (12), 8 females and 4 males, who took any amount of *Larrea* during the study period were identified. Twenty-three patients (23), 20 females and 3 males, who used any amount of *Larrea* in *Ricinus* oleum topically during the study period were identified.

RESULTS

A total of 12 patients had *Larrea* for internal use prescribed for them during the study period. A summary of patient data and levels of serum liver enzymes and other indicators of liver health is presented in Table 2 for the four patients with complete data available. One patient took relatively similar doses to these four cases but did not have follow-up blood chemistries and CBC. The remaining 8 patients took much smaller doses and/or blood values were not available. Some of the tests reported in Table 2 were chosen because these were used in one retrospective series of 13 hepatitis cases previously reported (Sheikh et al., 1997). In the

Table 2. Summary of Patient Data and Major Liver Function Tests

Patient	*Gender*	*Age*	*Dose*[a]	*Test date*	*AST in U/L*[b]	*ALT in U/L*[c]	*LDH in UI/L*[d]	*TB in mg/dL*[e]	*ALP in U/L*[f]
J.C.	F	49	32 mL	2/13/97	13	37	116	1.6	63
				8/1/97	21	24	196	1	45
S.R.	F	52	240 mL	11/26/96	16	23	103	0.7	50
				5/23/97	17	10	118	0.6	56
B.L.	M	53	34 mL	8/6/98	16	23	174	0.7	74
				11/13/98	32	34	146	0.6	81
D.D.	F	51	138 mL	1/14/97	15	14	126	0.8	65
				1/5/98	20	21	122	0.5	85

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; TB, total bilirubin.
[a]Maximum, total dose possible of *Larrea* tincture the patient took.
[b]Reference range is 0–41 U/L (except 2/13/97 test for patient J.C., when the range was 15–37 U/L).
[c]Reference range is 0–45 U/L (except 2/13/97 test for patient J.C., when the range was 30–65 U/L).
[d]Reference range is 100–230 U/L (except 2/13/97 test for patient J.C., when the range was 100–200 U/L).
[e]Reference range is 0.0–1.4 mg/dL (except 2/13/97 test for patient J.C., when the range was 0.1–1 mg/dL).
[f]Reference range is 20–130 U/L (except 2/13/97 test for patient J.C., when the range was 13–130 U/L).

patients in that study, most had elevated serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TB) levels. Liver biopsies were not performed on any of the cases presented here as none had any evidence of liver damage related to creosote bush ingestion.

Further information about the four patients with the most complete data and who took the largest doses are presented below.

Case 1 (J.C.)

This 49-year-old white woman was given a botanical formula for allergies containing 8% *Larrea* starting on March 24, 1997. The complete formula is listed in Table 3. She previously reported having tachycardia when taking a pseudoephedrine-containing product, so *Ephedra sinica* (ma haung, an ephedra-containing botanical often used to treat allergic patients) was not included. The patient purchased a total of 14 ounces of formula over a period of 4 months. The prescribed dose was 5 to 10 mL every 30 to 120 minutes. She reported dizziness when taking 10 mL of the formula by June 4, 1997 and was instructed to decrease the dose. On July 8, 1997 the patient reported that taking the formula four times daily did not help her allergies but she had no adverse effects. Therefore, assuming that the patient took all the formula she bought (and she may not have by her own admission), the maximum amount of *Larrea* tincture she took was 32 mL (1 ounce) over 3.5 months.

The patient was also taking esterified estro-

Table 3. Allergy Formula

Latin name	*Common name*	*Part used*[a]	*Percent of formula*	*Ethanol, glycerin content (%)*
Euphrasia spp.	Eyebright	Herba	16	25, 0
Sambucus nigra	Elder	Flos	16	25, 0
Solidago virgaurea	Goldenrod	Flos	16	45, 10
Urtica dioica	Stinging nettle	Herba	12	0, 75
Salvia officinalis	Sage	Herba	8	0, 75
Cochlearia amoracia	Horseradish	Radix	8	55, 10
Hydrastis canadensis	Goldenseal	Radix	8	65, 10
Larrea tridentata	Creosote bush	Herba	8	90, 0
Plantago major	Broadleaf plantain	Folia	8	30, 10

[a]Translation of Latin terms; Flos, flowers; Folia, leaves; Herba, aboveground parts of the plant; Radix, root.

gens and fluticasone nasal spray. Esterified estrogens were later discontinued and triple estrogen (80% estriol, 10% each estradiol, and estrone) and sublingual micronized progesterone were substituted. Her dietary supplements included calcium/magnesium, vitamin E, vitamin C with flavonoids, glucosamine sulfate, colloidal minerals, spirulina, vitamin B_{12}, folic acid, β-carotene, bromelain, quercetin, a separate complex herbal formula without *Larrea*, and *Equisetum arvense* (horsetail) herb glycerin extract. *Echinacea angustifolia* (purple coneflower) root tincture, *Taraxacum officinale* (dandelion) root tincture, and *Crataegus oxyacantha* (hawthorn) fluid extract were also prescribed during the period the patient was taking allergy formulas.

J.C. had an elevated total bilirubin level of 1.6 mg/dL on February 2, 1997 before she started taking *Larrea*. This level decreased to 1 mg/dL approximately 4 months after she started taking *Larrea*. She had a low white blood cell count (WBC) on February 13, 1997 of 2.68 thousands per cubic millimeter that increased to 3.1 by August 8, 1997. Her lymphocyte percentage was high at 48.5% and her granulocyte count low at 1.14 thousand per cubic millimeter on February 13, 1997 but both normalized by August 8, 1997. She had a lower serum iron level of 35 μg/dL on August 8, 1997. No other abnormalities were detected on routine testing. There was no indication of liver disease at any time; her serum liver enzyme levels are recorded in Table 2.

Case 2 (S.R.)

Starting on January 1, 1997 this 52-year-old white woman had the herbal formula described in Table 3 prescribed for her to reduce respiratory symptoms of allergies for which she was taking loratidine. The prescribed dose was 5 mL three times daily. She continued refilling this formula through May 1997. If she took the entire amount of allergy formula prescribed (which she stated she did and that her past history strongly supported), her maximum dose of *Larrea* tincture would have been 240 mL (8 ounces) over approximately 5 months.

S.R. was taking clonazepam and zolpidem, and started valproic acid in May 1997 as needed for manic symptoms. Thyroid United States Pharmacopoeia was prescribed to treat her hypothyroidism. Her nutritional supplements included coenzyme Q10, magnesium potassium taurine, lysine, vitamin C, flavonoids, a multivitamin/mineral, β-carotene, a complex botanical formula for respiratory infections, *Echinacea angustifolia* (purple coneflower) root tincture, spirulina, a botanical cough syrup, calcium, hydrolyzed fish protein, soy protein powder, phosphorylated serine and ethanolamine, *Silybum marianum* (milk thistle) seeds, a complex herbal formula, *Salvia officinalis* (sage) leaf glycerin extract, *Lactobacillus* and *Bifidobacterium*, and vitamin E.

Despite the concomitant use of potentially hepatotoxic medications there was no sign of liver disease at any time while S.R. was taking *Larrea*. The levels of her serum liver enzyme levels are reported in Table 2. She had a chronic low WBC (2.3 thousand per cubic millimeter on November 11, 1996 and 2.5 on May 5, 1997), low platelet count (123 thousand per cubic millimeter on November 11, 1996 and 133 on May 5, 1997), and low high-density lipoprotein (HDL) cholesterol level (42 mg/dL on November 26, 1996 and 40 on May 5, 1997). These were likely related to her medications. Her thyroid-stimulating hormone (TSH) level was high at 5.37 mIU/L on November 26, 1996 and 14.6 on May 15, 1997, necessitating alteration of her thyroid USP dose.

Case 3 (B.L.)

On August 4, 1998 this 53-year-old, afebrile, white man presented with painful axillary lymphadenopathy on the left side. He was given a botanical formula that is detailed in Table 4. Initially he was instructed to take 5 mL of this formula four times daily while applying oil of *Phytolacca decandra* topically, doing lymphatic massage, and taking a protein powder supplement. There was 90% improvement by August 14, 1998 and he stopped the formula.

The problem flared again on August 21, 1998 and continued despite reinstatement of the formula at a dose of 5 mL three times daily. Penicillin VK was prescribed at a dose of 500 mg four times daily for 10 days, along with bentonite clay packs, and *Larrea* in *Ricinus* oil top-

TABLE 4. LYMPHOGOGUE FORMULA

Latin name	*Common name*	*Part used*[a]	*Percent of formula*	*Ethanol, glycerin content (%)*
Ceanothus greggii	Red root	Radix	18	55, 10
Echinacea angustifolia	Echinacea	Radix	14	45, 10
Phytolacca decandra	Poke	Radix	11	55, 10
Arctium lappa	Burdock	Radix	11	35, 10
Fouquieria splendens	Ocotillo	Cortex	7	85, 10
Commiphora molmol	Myrrh	Resin	7	90, 0
Berberis aquifolium	Oregon grape	Cortex radii	7	45, 10
Taraxacum officinale	Dandelion	Radix	7	40, 10
Larrea tridentata	Creosote bush	Herba	7	90, 0
Baptisia tinctoria	Wild indigo	Radix	7	65, 10
Tabebuia spp.	Pau d'arco	Cortex	3	50, 10

[a]Translation of Latin terms: Cortex, bark; Cortex radii, bark of root; Herba, aboveground parts of the plant; Radix, root.

ically. The patient reduced the dose to only 5 mL once daily on approximately August 31, 1998 (the patient's memory was inexact as to the date). His maximum total internal dose of *Larrea* tincture was 34 mL (just over 1 ounce) over a period of approximately 40 days. Because the lesion did not completely resolve even with the antibiotic, the patient was referred for lymph node biopsy. Local spread of malignant melanoma was diagnosed, later shown to have metastasized to the lungs on a computed tomographic scan. The primary tumor was a subcutaneous nodule over the left scapula. Melanoma is known to take many years to develop and thus it is higly unlikely that *Larrea* had any role in the occurrence of this cancer, given that it was administered after metastasis of the primary tumor had already occurred.

On August 29, 1998, the patient had an elevated sedimentation rate of 38 mm/h, an elevated WBC of 14.3 thousand per cubic millimeter and a low lymphocyte percent of 12. On 9/29/98 the sedimentation rate was down to 11 while his WBC remained high at 11.6 with a granulocyte count of 8.6 thousand per cubic millimeter. The lymphocyte percent stayed low at 14 and the monocyte percent was now low at 9.7. Again there was no sign of liver damage related to his intake of *Larrea*. The specific values of his serum liver enzyme levels are given in Table 2.

Case 4 (D.D.)

On May 20, 1997 this 51-year-old female was given two weight management formulas, both containing *Larrea*. The basic formula for both is described in Table 5, although one version also

TABLE 5. WEIGHT MANAGEMENT FORMULA

Latin name	*Common name*	*Part used*[a]	*Percent of formula*	*Ethanol, glycerin content (%)*
Stellaria media	Chickweed	Herba	15	0, 75
Corynanthe yohimbe	Yohimbe	Cortex	15	50, 10
Fucus vesiculosus	Bladderwrack	Thallus	15	25, 10
Larrea tridentata	Creosote bush	Herba	10	90, 0
Trigonella foenum-graecum	Fenugreek	Semen	10	25, 10
Berberis aquifolium	Oregon grape	Radix	10	45, 10
Taraxacum officinale	Dandelion	Folia	10	30, 10
Salix nigra	Willow	Cortex	5	25, 0
Zingiber officinale	Ginger	Rhizoma	5	90, 0
Eleutherococcus senticosus	Eleuthero, Siberian ginseng	Radix	5	40, 0

[a]Translation of Latin terms: Cortex, bark; Folia, leaves; Herba, aboveground parts of the plant; Radix, root; Rhizoma, rhizome (underground stem); Semen, seed; Thallus, soft frond of a sea vegetable.

contained *Ephedra sinica* (ma huang) and *Cola vera* (kola nut). The dose in each case was 5 mL three times daily. On May 29, 1997, the patient adjusted the dose to 5mL daily of the formula without ma haung or kola nut in order to avoid any dependence on stimulants. She bought a total of 48 ounces of the formula for a total, maximum possible dose of *Larrea* of 138 mL (just over 4 ounces) over a period of approximately 3 to 4 months, although it is unclear when exactly the patient completed taking the formula.

She was taking no known hepatotoxic drugs and had no history of liver disease. Her nutritional supplements included garlic capsules, soy protein powder, a complex botanical formula without *Larrea*, vitamin C, a multivitamin/mineral, vitamin E, and calcium/magnesium. No sign of liver injury appeared at any time during the course of her use of the weight management formula containing *Larrea*. Her serum liver enzyme levels are reported in Table 2. She had an elevated total cholesterol level of 228 mg/dL on January 14, 1997 and elevated low-density lipoprotein (LDL) cholesterol level of 159 mg/dL. Her neutrophil percent was low at 37 on January 14, 1997 while her lymphocyte percent was high at 58. One year later, on January 5, 1998, her total cholesterol level was 264 mg/dL, her triglyceride level was elevated at 266 mg/dL, and her LDL level was 159 mg/dL. Her neutrophil and lymphocyte percentages had normalized.

Other patients

One patient (J.H.) first took a formula containing *Larrea* on February 21, 1996. Table 6 lists the components of her formula, used as part of therapy for a dental infection. She used 5 mL every 2 to 3 hours as needed. The same prescription was made for other dental infections on December 9, 1996 and April 28, 1997. Her total maximum possible dose of *Larrea* was therefore 215 mL periodically over a period of more than 14 months. The patient moved out of state and so it was unclear if she continued using the *Larrea*-containing formula beyond approximately 15 months. She had no history of liver disease and serum liver enzyme levels measured on January 29, 1996 showed no elevations. Follow-up laboratory work was not available. She developed no signs or symptoms of liver damage.

The remaining eight patients did not have complete documentation or took less than 30 mL of *Larrea* tincture. These patients are summarized in Table 7. None of these patients developed clinical symptoms suggestive of *Larrea*-induced hepatotoxicity. No other adverse effects could be attributed to the *Larrea* in any case.

Larrea in *Ricinus* oil for topical use during the study period was prescribed for a group of 20 female and 3 male adult patients. Indications included dysmenorrhea, cancer, pain, benign parotid mass, myalgia, and genital herpes sim-

Table 6. Herbal Antibiotic Formula

Latin name	*Common name*	*Part used*[a]	*Percent of formula*	*Ethanol, glycerin content (%)*
Echinacea angustifolia	Echinacea	Radix	18	45, 10
Larrea tridentata	Creosote bush	Herba	18	90, 0
Allium sativum	Garlic	Bulbus	18	0, 75
Hydrastis canadensis	Goldenseal	Radix	9	65, 10
Commiphora molmol	Myrrh	Resin	9	90, 0
Berberis aquifolium	Oregon grape	Radix	9	45, 10
Cochlearia amoracia	Horseradish	Tuber	5	55, 10
Phytolacca decandra	Poke	Radix	5	55, 10
Baptista tinctoria	Wild indigo	Radix	5	65, 10
Eucalyptus globulus	Eucalyptus	Folia	5	45, 10

[a]Translation of Latin terms: Bulbus, bulb; Herba, aboveground parts of the plant; Radix, root; Tuber, underground storage organ.

TABLE 7. PATIENTS RECEIVING ULTRA-LOW DOSES OF *LARREA TRIDENTATA* TINCTURE

Patient	*Age*	*Gender*	*Maximum possible amount of* Larrea *(mL)*[a]	*Concomitant potentially hepatotoxic drugs*
S.F.	47	F	22	Acetaminophen
J.R.	39	F	24	None
T.D.	26	M	20	None
L.Y.	55	M	12	None
K.A.	48	F	<5	None
C.W.	47	F	<5	None
K.G.	38	F	<5	Acetaminophen, venlafaxine
M.L.	42	M	<5[b]	None

[a]Taken over a period of weeks to months.
[b]This patient reported taking significant amounts (more than 100 mL in a 3-month period) of a tincture of *Larrea tridentata* that he prepared himself in combination with two other botanicals. He developed no sign of liver disease at any point.

plex. No patient reported an adverse effect except for one woman who used it repeatedly in combination with an oil infusion of *Hypericum perforatum* (St. John's wort) flowers for genital herpes. The use of the oils caused a spreading of the lesions, as is known to occur with medications of any kind in an oil suspension. This was seen as a prescribing error and not an adverse effect of the herbs in question, given that tinctures of the two herbs have been observed in practice to have a definitive healing effect. Acyclovir led to rapid reduction in symptoms in the patient cited above. No patient showed any sign of organ damage while using topical *Larrea* in *Ricinus* oil.

DISCUSSION

Although it is limited in scope, our report suggests low does (<1 mL daily of tincture) of *Larrea* are safe for internal use when recommended by an experienced botanical prescriber in a naturopathic clinical context. Topical application of this plant in *Ricinus* oil was also found to be without negative effect directly attributed to the *Larrea.* These analyses are not intended to document efficacy.

All of the materials were prepared and dispensed by the prescribing physicians themselves. This eliminates the possibility of adulteration or misidentification, incidental or intentionally, that is unfortunately common in the rapidly expanding mass market for botanical medicines. It also helps ensure that a high-quality source material is utilized, although it would likely be beneficial to implement chromatographic analysis of multiple constituents in each batch to confirm this. Our methods probably correspond more closely with medicinal use of *Larrea* tea by Native Americans than taking encapsulated, powdered herb. Nevertheless, there is still some difference between the 90% ethanol extract utilized in our study and traditional aqueous extracts. The lack of toxicity found in our study correlates with the lack of reports of toxicity of tea. Overall the main conclusion again appears to be that avoiding overdoses of any form is likely to be the most important factor in preventing adverse effects.

The use of complex botanical mixtures or formulae is a traditional practice in naturopathic and herbal medicine. This has been called polypharmacy and is looked on unfavorably by some medical practitioners despite the fact that many patients are taking more than one pharmaceutical drug at a time (Colley and Lucas, 1993). For example, one study of elderly people living in residential care facilities found that the average number of prescriptions per resident was five (Williams et al., 1999). Clinical experience confirms that polypharmaceutical prescription of herbs is an effective and safe means of practice, although it has been poorly investigated in the Western world. In contrast, multi-ingredient patent formulae are commonly used in Traditional Chinese Medicine

and have been the subject of innumerable clinical trials in China. By limiting intake of any single ingredient in multiherb Chinese or other formulas, the risk of causing toxic reactions is lowered. The belief is that the actions of the totality of the plant are synergistic and account for therapeutic activity despite what would be insufficient doses (but being small, unlikely to cause toxicity) of any one constituent in isolation. Synergistic effects may even decrease the toxicity of plants that are more dangerous in isolation (Johns, 1990). Although this type of prescribing might be extremely dangerous using pharmaceutical compounds, in our experience, the combination of whole-plant extracts tends to be safer than the use of single herbs.

One source of information on this practice can be found in the "approved fixed combinations" of the Commission E monographs (Bluementhal et al., 1998). Here we find, for example, a combination of *Mentha* × *piperita* (peppermint) leaf, *Carum carvi* (caraway) seed, *Matricaria recutita* (German chamomile) flower and *Citrus aurantium* (bitter orange) peel is approved for treating patients with dyspepsia by the official German government committee on botanical medicine. Each herb has a separate history of use for this condition, although in this set combination, at most 40% of each dose of each single herb is given. Nevertheless, efficacy does not seem to be lost.

The retrospective nature of the study, the limited number of cases, and lack of a control group weaken the strength of our findings. However, no patient for whom *Larrea* was prescribed during the study was excluded from the analysis, thereby reducing selection bias. The study was also based in everyday practice, meaning that each patient was taking a variety of other supplements with few similarities between them. Additionally, introduction of *Larrea* into each patient's therapy was not necessarily done while other treatments were held constant. Although these methodological weaknesses are generally considered severely limiting, we believe that in the realm of safety of typical herbal prescribing they are not as important. This is because the real-world conditions of the study strengthen the conclusion that *Larrea* as actually prescribed (as compared to the relatively artificial setting of a single-agent, controlled, clinical trial) is an acceptable practice. Thus, while it is difficult to conclude definitely from this study alone that *Larrea* is safe, the preliminary conclusion may be drawn that when 90% ethanol extracts internally or *Ricinus* oil extracts topically of this plant were used in the doses described herein in combination with a variety of natural products, no signs of the liver damage reported elsewhere were encountered in our practice. These findings also document a lack of general toxicity and suggest previously reported cases may be of an idiosyncratic nature, based on the rare susceptibility of individual patients.

Clearly, prospective studies are needed to confirm the safety of *Larrea*. Such studies are urged to document efficacy and safety for this useful natural resource.

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